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(54) Title: ORGANOGERMANIUM COMPOUNDS AND METHODS FOR THEIR USE

(57) Abstract: The invention provides a method for enantioselectively reducing a prochiral carbon centred radical having one or more electron donor groups attached directly to the central prochiral carbon atom of the radical, and/or attached to a carbon atom within 1 to 4 atoms of the central prochiral carbon atom, comprising treating said radical with a chiral non-racemic organogermanium hydride in the presence of a Lewis acid. The invention also provides a novel class of chiral non-racemic organogermanium hydrides and a method of preparing chiral non-racemic organogermanium compounds.

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ORGANOGERMANIUM COMPOUNDS AND METHODS FOR THEIR USE

FIELD OF THE INVENTION

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The present invention relates generally to reductive methods useful in chemical synthesis. In particular, the invention relates to enantioselective reductive methods using chiral organogermanium hydrides, to a novel class of chiral organogermanium hydrides, and to a method of preparing chiral organogermanium compounds.

10

BACKGROUND

The scientific literature contains numerous reports of free-radical reactions proceeding with diastereocontrol, (see for example, reviews such as Curran, D.P., *et al*,
15 *Stereochemistry of Radical Reactions*, VCH, Weinheim, 1995; Smadja, W., *et al* *Synlett*, 1994, 1; Porter, N.A., *et al*, *Acc.Chem. Res.*, 1991, 24, 296; and Sibi, M., *et al*, *Acc. Chem. Res.*, 1999, 32, 163). However, there are relatively very few examples of free-radical reactions which proceed with genuine enantiocontrol. The majority of the examples that demonstrate enantioselective outcomes involve the use of chiral auxiliaries
20 and, as a result, are actually further examples of diastereo-selectivity in free-radical chemistry.

Of the remaining few reports, the introduction of asymmetry in the substrate has been achieved through the use of chiral Lewis acid mediation (see for example, Guindon, Y., *et al*,
25 *Tetrahedron Lett.*, 1990, 31, 2845; Guindon, Y., *et al*, *J. Am. Chem. Soc.*, 1991, 113, 9701 and Renaud, P., *et al* *Angew. Chem. Int. Ed.*, 1998, 37, 2563), or by a chiral reagent through the use of chiral ligands on the tin atoms in suitably constructed stannanes (Schumann, H., *et al*, *J. Organomet. Chem.* 1984, 265, 145; Curran, D. P., *et al*, *Tetrahedron; Asymmetry*, 1996, 7, 2417; Blumstein, M., *et al*, *Angew. Chem. Int. Ed.*,
30 1997, 36, 235 and Scharzhkopf, K., *et al*, *Eur. J. Chem.*, 1998, 177).

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Recently, chiral non-racemic stannanes, in conjunction with appropriate chiral or achiral Lewis acids, have been shown to reduce a variety of prochiral radicals with enhanced enantioselectivity when compared to results obtained in the absence of Lewis acid mediation (*Chem Commun.* 1999, 1665-1666).

5

While providing effective means to enantioselectively prepare chiral compounds, the enantioselective reducing capacity of chiral non-racemic stannanes is limited. In particular, inherently high hydrogen transfer rate constants preclude such stannanes from reducing several classes of prochiral radicals with acceptable chiral discrimination.

10 Furthermore, the chiral recognition of the stannane reducing agents is limited due the inability for such agents to sustain chirality at the tin atom.

Accordingly, there is a need to develop a more versatile reducing agent for use in the enantioselective preparation of chiral compounds.

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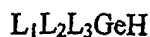
SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a method for enantioselectively reducing a prochiral carbon centred radical having one or more electron donor groups attached
20 directly to the central prochiral carbon atom of the radical, and/or attached to a carbon atom within 1 to 4 atoms of the central prochiral carbon atom, comprising treating said radical with a chiral non-racemic organogermanium hydride in the presence of a Lewis acid.

25 Preferably, the electron donor group is attached directly to the central prochiral carbon atom or to a carbon atom within 1 or 2 atoms of the central prochiral carbon atom.

In a second aspect, the present invention provides a chiral non-racemic organogermanium hydride of general formula (I):

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(I)

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where L_1 , L_2 and L_3 are organic substituents which may be the same or different, and where at least one of L_1 , L_2 and L_3 is chiral, with the proviso that formula (I) is not 4-*tert*-butyl-3,5-dithia-4-germacyclohepa[2,1-*a*; 3,4-*a'*]dinaphthalene or 4-*tert*-butyl-2,6-bis(trimethylsilyl)-3,5-dithia-4-germacyclohepa[2,1-*a*; 3,4-*a'*]dinaphthalene.

5

It is to be understood that while the second aspect of the invention is not intended to encompass known chiral non-racemic organogermanium hydride reagents, the first aspect of the invention relates to the use of any suitable chiral non-racemic organogermanium hydride reagents, even those which may have been described in the prior art.

10

In a particular embodiment, the invention is directed towards a method of preparing optically enhanced α or β - amino acids by treatment of a prochiral amino acid carbon centred radical with a chiral non-racemic organogermanium hydride in the presence of a Lewis acid, wherein the central prochiral carbon atom is an α - carbon atom of an α - amino acid or a β - carbon atom of an α -amino acid.

15

A limited number of chiral germanium hydride reagents have been used in the past to make chiral compounds, however such compounds have afforded poor enantioselectivity.

It has now been found that chiral non-racemic organogermanium hydride reagents can be used in conjunction with a Lewis acid to enantioselectively prepare chiral compounds. The germanium reagents demonstrate reduced hydrogen transfer rate constants compared with their stannane counterparts, the effect of which provides for superior kinetic control over the reduction chemistry. Advantageously, the superior kinetic control can enable the range of suitable prochiral substrates to be extended beyond that available to stannane analogues. Furthermore, the germanium reagents are able to sustain chirality at the germanium atom and therefore demonstrate the potential to provide enhanced chiral recognition. In this case, the structural integrity germanium reagents should be sufficiently stable so as not to racemise during the reduction reaction.

25

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DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "prochiral carbon centred radical" is a radical of formula $R_1R_2R_3C\cdot$, wherein each R residue is different and is not hydrogen. Accordingly, the central prochiral carbon atom is the carbon atom to which the R residues are attached.
5 Reduction of the prochiral carbon centred radical with a hydrogen atom donor affords the chiral compound $R_1R_2R_3CH$. The present invention thus relates to the enantioselective preparation of chiral compounds.

10 The prochiral carbon centred radical can be generated from any suitable radical precursor using methods known in the art. Exemplary radical precursors include aryl, eg phenyl, selenides; aryl, eg phenyl, sulfides; aryl, eg phenyl, tellurides; xanthates; thionoformates and Barton esters (see for example B. Giese, *Radicals in Organic Synthesis – Formation of C-C Bonds* (1986) Pergamon Press, Oxford, the contents of which are incorporated herein
15 by reference). Particularly suitable radical precursors for generating the prochiral carbon centred radicals for use in the invention are tertiary chiral halosubstrates, ie $R_1R_2R_3C$ -halogen, where R_1 - R_3 are different and not hydrogen and halogen is chlorine, bromine or iodine, preferably bromine.

20 The prochiral carbon centred radicals which can be reduced by the methods of the invention include radicals which bear one or more electron donator groups directly on the prochiral central carbon atom and/or attached to a carbon atom α , β , γ , or δ to the central prochiral carbon atom, ie, within 1, 2, 3 or 4 atoms, preferably within 1 or 2 atoms. Suitable electron donator groups include those containing an electron donator atom such as
25 oxygen, nitrogen, and/or sulfur and which will not be affected by the organogermanium hydride. One example of an electron donator group is a carbonyl group $C(=O)$, present, as for example, in aldehydes, ketones, carboxy acid, carboxy esters, carboxy amides, anhydrides, lactones, lactams, carbonates, carbamates and thioesters etc. Other electron donator groups include, thioalkyl groups, amines (unsubstituted or substituted once or
30 twice by, for example, a group selected from alkyl, acyl and aryl), hydroxy groups and ethers (eg alkyl and aryl). A preferred electron donator is a carbonyl group. Preferably the

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carbonyl group is adjacent to, ie α - to the chiral carbon to be reduced. Expressed in another way, the prochiral carbon centred radical has at least one electron donator atom within 5 atoms (ie 1, 2, 3; 4, or 5) of the central prochiral carbon atom. It will be recognised that some electron donator groups may contain one or more electron donating atoms, eg carboxy acid, carboxy ester, thioester, carboxy amide. A prochiral carbon centred radical may also contain more than one electron donating group attached to the central prochiral atom.

Exemplary prochiral carbon centred radicals include those of the formula $R_1R_2R_3C\cdot$, wherein R_1 - R_3 are different (and not hydrogen) and are independently selected from alkyl, alkenyl, alkynyl, aryl, heterocyclyl, acyl, amino, substituted amino, carboxy, anhydride, carboxy ester, carboxy amide, lactone, lactam, thioester, formyl, optionally protected hydroxy, thioalkyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heterocyclyloxy; or alternatively, any two of R_1 - R_3 can together, with the central prochiral carbon atom, form a mono- or poly- cyclic group or fused polycyclic group including as cycloalkyl, cycloalkenyl, cycloalkynyl, a lactone, a lactam, cyclic anhydride, or heterocyclyl and bi-, tri- and tetracyclic fused combinations thereof. When the method of the present invention comprises a Lewis acid, at least one of R_1 - R_3 , or a cyclic group formed by any two of R_1 - R_3 , contains an electron donator atom within 1 to 5 atoms of the prochiral central carbon atom to be reduced. It will be understood that a radical precursor may contain more than one prochiral radical precursor sites and that reduction may therefore occur at one or more of these sites.

In a preferred embodiment, at least one of R_1 - R_3 is an optionally substituted aryl or heteroaryl group. In another preferred embodiment at least one of R_1 - R_3 is an optionally substituted alkyl, alkenyl, or alkynyl group. In another embodiment, at least one of R_1 - R_3 is a ketone, aldehyde, carboxy acid, carboxy ester, carboxy amide, anhydride, lactone, lactam or thioester, or two of R_1 - R_3 together with the central prochiral carbon atom form a cyclic anhydride, lactam or lactone.

30

Preferred "ketones" have the formula $-C(O)-R$ wherein R can be any residue, having a

carbon atom covalently bonded to the carbonyl group, such as alkyl, alkenyl, alkynyl and aryl. An R group may have one or more carbon atoms optionally replaced with one or more heteroatoms to form, for example, heterocyclyl.

Preferred "carboxy esters" have the formula $\text{-CO}_2\text{R}$ wherein R can be any residue, having a
5 carbon atom covalently bonded to the non-carbonyl oxygen atom, for example, alkyl, alkenyl, alkynyl or aryl. An R group may have one or more carbon atoms optionally replaced with one or more heteroatoms, such that R is for example heterocyclyl.

Preferred "carboxy amides" have the formula $\text{CO}_2\text{NRR}'$ wherein R and R' are
10 independently selected from hydrogen and any residue having a carbon atom covalently bonded to the nitrogen atom such as alkyl, alkenyl, alkynyl or aryl. An R or R' group may have one or more carbon atoms optionally replaced with one or more heteroatoms to form, for example, heterocyclyl.

15 Preferred "thioesters" have the formula -C(O)SR wherein R can be any residue having a carbon atom covalently bonded to the sulfur atom, such as alkyl, alkenyl, alkynyl or aryl. An R group may have one or more carbon atoms optionally replaced with one or more heteroatoms to form, for example, heterocyclyl.

20 Preferred anhydrides contain the moiety -C(O)-OC(O)- and may be cyclic or acyclic. Preferred acyclic anhydrides contain the moiety -C(O)-O-C(O)-R wherein R can be any residue, such as alkyl, alkenyl, alkynyl or aryl. An R group may have one or more carbon atoms optionally replaced with one or more heteroatoms to form, for example, heterocyclyl. Preferred cyclic anhydrides contain the moiety $\text{-C(O)-O-C(O)-(CH}_2\text{)}_n\text{-}$
25 wherein n is ≥ 1 , eg. 1, 2, 3, 4, 5 or 6.

Lactones are cyclic residues containing the moiety -C(O)O- . Preferred lactones have the formula -C(O)O-R- wherein R can be any residue, having a carbon atom covalently bonded to the non-carbonyl oxygen atom, eg alkylene, alkenylene, alkynylene. An R
30 group may have one or more carbon atoms optionally replaced by one or more heteroatoms. Preferred lactones contain the moiety $\text{-C(O)-O- (CH}_2\text{)}_n\text{-}$ wherein n is ≥ 2 ,

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eg., 2, 3, 4, 5 or 6.

Lactams are cyclic residues containing the moiety $-C(O)-N(R')-R-$ wherein R' can be
5 hydrogen or any hydrocarbon residue such as alkyl, acyl, aryl or alkenyl. $-R-$ can be any
hydrocarbon residue having a carbon atom covalently bonded to the nitrogen atom such as
alkylene, alkenylene or alkynylene. An R' or R group may have one or more carbon atoms
optionally replaced by one or more heteroatoms. Preferred lactams contain the moiety $-$
 $C(O)-N(R')-(CH_2)_n-$ wherein n is ≥ 2 , eg., 2, 3, 4, 5 or 6.

10

As used herein, the term "alkyl", denotes straight chain, branched or cyclic hydrocarbon
residues, preferably C_{1-20} alkyl, eg C_{1-10} or C_{1-6} . Examples of straight chain and branched
alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl,
isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethyl-propyl, hexyl, 4-methylpentyl, 1-
15 methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-
dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-
trimethylpropyl, heptyl, 5-methoxyhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-
dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-
dimethyl-pentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, 6-
20 methylheptyl, 1-methylheptyl, 1,1,3,3-tetramethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-
methyl-octyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-, 2- or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-,
6-, 7- and 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-, 3- or 4-propylheptyl,
undecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-ethylnonyl,
1-, 2-, 3-, 4- or 5-propyloctyl, 1-, 2- or 3-butylheptyl, 1-pentylhexyl, dodecyl, 1-, 2-, 3-, 4-,
25 5-, 6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-,
5- or 6-propylnonyl, 1-, 2-, 3- or 4-butyloctyl, 1-2-pentylheptyl and the like. Examples of
cyclic alkyl include mono- or polycyclic alkyl groups such as cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.
Where an alkyl group is referred to generally as "propyl", "butyl" etc, it will be understood
30 that this can refer to any of straight, branched and cyclic isomers. An alkyl group may be
optionally substituted by one or more optional substituents as herein defined. Accordingly,

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"alkyl" as used herein is taken to refer to optionally substituted alkyl. Cyclic alkyl may refer to monocyclic alkyl or, polycyclic fused or non-fused carbocyclic groups.

The term "alkenyl" as used herein denotes groups formed from straight chain, branched or
5 cyclic hydrocarbon residues containing at least one carbon to carbon double bond including ethylenically mono-, di- or poly-unsaturated alkyl or cycloalkyl groups as previously defined, preferably C₁₋₂₀ alkenyl (eg C₁₋₁₀ or C₁₋₆). Examples of alkenyl include vinyl, allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl,
10 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1,4-pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl. An alkenyl group may be optionally substituted by one or more optional substituents as herein defined. Accordingly, "alkenyl"
15 as used herein is taken to refer to optionally substituted alkenyl. Cyclic alkenyl may refer to monocyclic alkenyl or, polycyclic fused or non-fused alkenyl carbocyclic groups.

As used herein the term "alkynyl" denotes groups formed from straight chain, branched or cyclic hydrocarbon residues containing at least one carbon-carbon triple bond including
20 ethynically mono-, di- or poly-unsaturated alkyl or cycloalkyl groups as previously defined. Unless the number of carbon atoms is specified the term preferably refers to C₁₋₂₀ alkynyl. Examples include ethynyl, 1-propynyl, 2-propynyl, and butynyl isomers, and pentynyl isomers. An alkynyl group may be optionally substituted by one or more optional substituents as herein defined. Accordingly, "alkynyl" as used herein is taken to refer to
25 optionally substituted alkynyl. Cyclic alkynyl may refer to monocyclic alkynyl or, polycyclic fused or non-fused alkynyl carbocyclic groups.

The terms "alkoxy", "alkenoxy", "alkynoxy", "aryloxy" and "heterocycloxy" respectively denote alkyl, alkenyl, alkynyl, aryl and heterocyclyl groups as hereinbefore defined when
30 linked by oxygen.

The term "halogen" denotes chlorine, bromine or iodine.

The term "aryl" denotes single, polynuclear, conjugated and fused residues of aromatic hydrocarbon ring systems. Examples of aryl include phenyl, biphenyl, terphenyl, quaterphenyl, naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl, pyrenyl, idenyl, azulenyl, chrysenyl. Aryl may be optionally substituted as herein defined and thus "aryl" as used herein is taken to refer to optionally substituted aryl.

- 10 The term "heterocyclic" denotes mono- or polycarbocyclic groups, which may be fused or conjugated, aromatic (heteroaryl) or non-aromatic, wherein at least one carbon atom is replaced by a heteroatom, preferably selected from nitrogen, sulphur and oxygen. Suitable heterocyclic groups include N-containing heterocyclic groups, such as:
- unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, imidazoliny, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl or tetrazolyl;
- saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as, pyrrolidinyl, imidazolidinyl, piperidyl, pyrazolidinyl or piperazinyl;
- condensed saturated or unsaturated heterocyclic groups containing 1 to 5 nitrogen atoms, such as, indolyl, isoindolyl, indoliny, isoindoliny, indoliziny, isoindoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, puriny, quinazoliny, quinoxaliny, phenanthradiny, phenathroliny, phthalaziny, naphthyridiny, cinnoliny, pteridiny, perimidiny or tetrazolopyridazinyl;
- saturated 3 to 6-membered heteromonocyclic groups containing 1 to 3 oxygen atoms, such as tetrahydrofuranyl, tetrahydropyranyl, tetrahydrodioxiny,
- unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, such as, pyranyl, dioxiny or furyl;
- condensed saturated or unsaturated heterocyclic groups containing 1 to 3 oxygen atoms, such as benzofuranyl, chromenyl or xanthenyl;
- 30 unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms, such as, thienyl or dithiolyl;

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- unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, oxazolyl, oxazolinyl, isoxazolyl, furazanyl or oxadiazolyl;
saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, morpholinyl;
- 5 unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, benzoxazolyl or benzoxadiazolyl;
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolyl, thiazolinyl or thiadiazolyl;
saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolidinyl, thiomorphinyl; and
- 10 unsaturated condensed heterocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, benzothiazolyl or benzothiadiazolyl.

A heterocyclic group may be optionally substituted by an optional substituent as described
15 herein.

- The term "acyl" denotes a group containing the moiety C=O (and not being a carboxylic acid, ester or amide or thioester). Preferred acyl includes C(O)-R, wherein R is hydrogen or an alkyl, alkenyl, alkynyl, aryl or heterocyclyl, residue, preferably a C₁₋₂₀ residue.
- 20 Examples of acyl include formyl; straight chain or branched alkanoyl such as, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl and icosanoyl; cycloalkylcarbonyl such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl; aroyl such as benzoyl, toluoyl and naphthoyl; aralkanoyl such as phenylalkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutyl, phenylpentanoyl and phenylhexanoyl) and naphthylalkanoyl (e.g. naphthylacetyl, naphthylpropanoyl and naphthylbutanoyl); aralkenoyl such as phenylalkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl and phenylhexenoyl) and naphthylalkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl and naphthylpentenoyl); aryloxyalkanoyl such as
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phenoxyacetyl and phenoxypropionyl; arylthiocarbamoyl such as phenylthiocarbamoyl; arylglyoxyloyl such as phenylglyoxyloyl and naphthylglyoxyloyl; arylsulfonyl such as phenylsulfonyl and naphthylsulfonyl; heterocycliccarbonyl; heterocyclicalkanoyl such as thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, 5 thiazolylacetyl, thiadiazolylacetyl and tetrazolylacetyl; heterocyclicalkenoyl such as heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl and heterocyclichexenoyl; and heterocyclicglyoxyloyl such as thiazolylglyoxyloyl and thienylglyoxyloyl. Acyl also refers to optionally substituted acyl.

10 The term "acyloxy" refers to acyl, as herein before defined, when linked by oxygen.

In this specification "optionally substituted" is taken to mean that a group may or may not be further substituted or fused (so as to form a condensed polycyclic group) with one or more groups selected from alkyl, alkenyl, alkynyl, aryl, hydroxy, alkoxy, alkenyloxy, 15 aryloxy, nitro, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylamino, diarylamino, acyl, acylamino, diacylamino, acyloxy, alkylsulphonyloxy, arylsulphenyloxy, heterocyclyl, heterocycloxy, heterocyclamino, carboalkoxy, carboaryloxy, alkylthio, arylthio, acylthio, cyano, nitro, sulfate and phosphate groups.

20

Preferred optional substituents include alkyl, (eg C₁₋₆ alkyl such as methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), hydroxyalkyl (eg hydroxymethyl, hydroxyethyl, hydroxypropyl), alkoxyalkyl (eg methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl etc) alkoxy (eg 25 C₁₋₆ alkoxy such as methoxy, ethoxy, propoxy, butoxy, cyclopropoxy, cyclobutoxy), halo, trifluoromethyl, trichloromethyl, tribromomethyl. hydroxy, phenyl (which itself may be further substituted), benzyl (wherein benzyl itself may be further substituted), phenoxy (wherein phenyl itself may be further substituted), benzyloxy (wherein benzyl itself may be further substituted), amino, alkylamino (eg C₁₋₆ alkyl, such as methylamino, 30 ethylamino, propylamino etc), dialkylamino (eg C₁₋₆ alkyl, such as dimethylamino, diethylamino, dipropylamino), acylamino (eg NHC(O)CH₃), phenylamino (wherein

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phenyl itself may be further substituted), nitro, formyl, -C(O)-alkyl (eg C₁₋₆ alkyl, such as acetyl), O-C(O)-alkyl (eg C₁₋₆ alkyl, such as acetyloxy), benzoyl (wherein the phenyl group of the benzoyl may itself be further substituted), carbonyl, (ie replacement of CH₂ with C=O) CO₂H, CO₂alkyl (eg C₁₋₆ alkyl such as methyl ester, ethyl ester, propyl ester, butyl ester), CO₂phenyl (wherein phenyl itself may be further substituted), CONH₂, CONHphenyl (wherein phenyl itself may be further substituted), CONHbenzyl (wherein benzyl itself may be further substituted), CONHalkyl (eg C₁₋₆ alkyl such as methyl ester, ethyl ester, propyl ester, butyl amide), CONHdialkyl (eg C₁₋₆ alkyl).

10 As used herein, "heteroatom" refers to any atom other than a carbon atom which may be a ring-member of a cyclic organic compound. Examples of suitable heteroatoms include nitrogen, oxygen, sulfur, phosphorous, boron, silicon, arsenic, selenium and tellurium.

The reductive method of the invention is typically carried out for a time and under
15 conditions sufficient to effect enantioselective reduction of a suitable prochiral radical precursor by hydrogen. Suitable reaction temperatures, solvents and quantities of stannane and initiator for free radical reductions are known in the art (see for example V.T. Perchyonok *et al*, *Tetrahedron. Lett.*, 1998, 39, 5437 and references cited therein). Preferred solvents include hydrocarbon solvents, eg toluene. The reduction is preferably
20 carried out at temperature less than 0°C, preferably less than about -30°C, more preferably at about -78°C. Preferably, the reagents used and the reaction conditions employed are substantially anhydrous. Exemplary initiators include those which are reactive at these temperatures such as AMBM (*Tetrahedron Lett.*, 1997, 38, 6301); 9-BBN (*Tetrahedron Lett.*, 1998, 39, 5437), 9-alkyl-9-BBN, (eg alkyl = ethyl, propyl, butyl etc); and Et₃B/O₂.

25

Exemplary chiral non-racemic organogermanium hydrides for use in accordance with the method of the invention have the formula L₁L₂L₃GeH, wherein L₁, L₂ and L₃ are different (ie. L₁ ≠ (L₂ or L₃) and L₂ ≠ L₃). Alternatively, L₁-L₃ may be the same or different wherein at least one of L₁-L₃ has a chiral centre. Accordingly, chiral non-racemic organogermanium
30 hydrides suitable for use in the method of the invention can derive their chirality from a chiral germanium atom, or from at least one chiral ligand attached to a non-chiral

- 13 -

germanium atom, or from at least one chiral ligand attached to a chiral germanium atom. Suitable achiral ligands include, but are not limited to, optionally substituted aryl (eg. optionally substituted phenyl, and naphthyl) and optionally substituted achiral alkyl (eg. methyl, and butyl) as defined previously. Suitable chiral ligands include, but are not limited to, menthyl and fused polycyclics such as 3 α -cholestane and those derived from cholic acid, eg. 3 α -24-norcholanyl and 7 α -24-norcholanyl (Schiesser et al, *Aust. J. Chem.*, 2001).

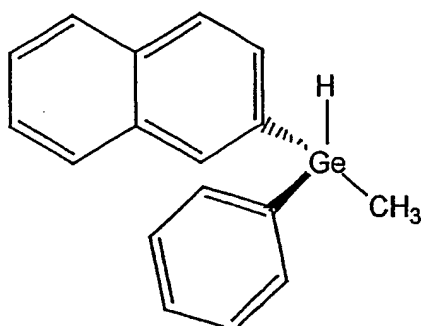
As used herein the term "chiral germanium atom" or "chiral atom" denotes an atom which has different substituents attached to it, and which can form part of a molecule to render the molecule non-superimposable on its mirror image.

As used herein the term "non-chiral germanium atom" denotes a germanium atom that has at least two substituents attached to it which are the same. Accordingly, a non-chiral germanium atom may form part of a molecule that can be superimposed on its mirror image.

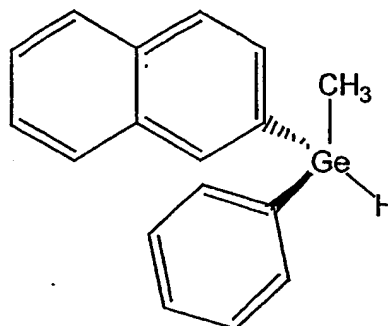
As used herein the term "chiral ligand" or "chiral organic substituent" denotes an organic molecule that is not superimposable on its mirror image.

Examples of chiral non-racemic organogermanium hydrides that may be used in accordance with the method of the invention include, but are not limited to, (*R*)- and (*S*)-methyl(2-naphthyl)phenylgermanium hydride (a) and (b) (and related compounds), which can be prepared by the method of Carré (*J. Organomet. Chem.*, 1970, 25, 395), [(1*R*,2*S*,5*R*)-menthyl]diphenylgermanium hydride (c) and its enantiomer [(1*S*,2*R*,5*S*)-methyl]diphenylgermanium hydride (c'), prepared as described below, 3 β -dimethylgermyl-5 α -cholestane (d) (and the 3 α analogue), 3 α -dimethylgermyl-5 α -cholestane (d), prepared in a similar manner to that described for (c), and bis[(1*R*,2*S*,5*R*)-menthyl]phenylgermanium hydride (e), prepared in a similar manner to that described for (c).

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(a)



(b)

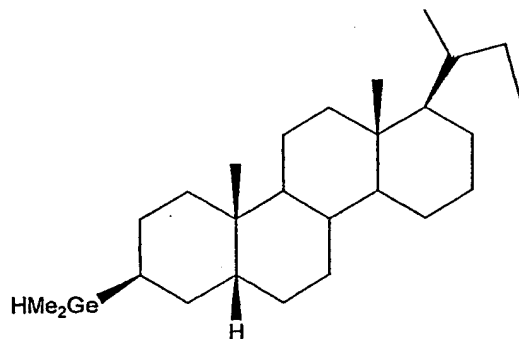
menPh₂GeH

(c)

enan-menPh₂GeH

(c')

5



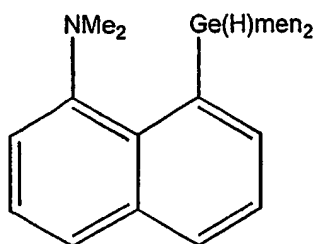
(d)

men₂PhGeH

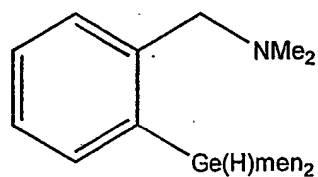
(e)

Other suitable chiral non-racemic organogermanium hydrides include (f) and (g), which can be prepared by reaction of the appropriate aryl lithium with bis[(1*R*,2*S*,5*R*)-menthyl]phenylgermanium chloride followed by LiAlH₄ reduction, where bis[(1*R*,2*S*,5*R*)-menthyl]phenylgermanium chloride is prepared in a similar manner to (1*R*, 2*S*, 5*R*)-menthyldiphenylgermanium bromide as described below. Other suitable aryl germanium hydrides can be made in an analogous manner. Further examples of a suitable organogermanium hydride include (f) and (g), where one of the menthyl groups is replaced by an aryl or alkyl substituent as defined previously (both diastereoisomers).

- 15 -

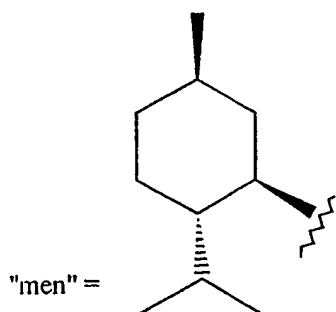


(f)

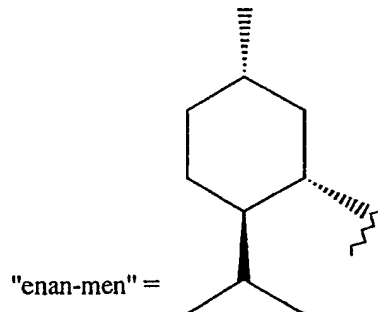


(g)

5 In the above structures,

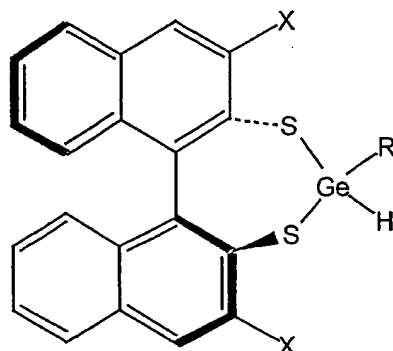


and



10 In addition, chiral non-racemic germanium hydrides include (h) and related compounds which can be prepared from 1,1'-thiobinaphthol as described by Gualtieri (PhD Thesis, The University of Pittsburgh, 2000), in which the ligand (R) is alkyl, or optionally substituted aryl as defined previously, and X is alkyl or trialkylsilyl.

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(h)

Lewis acids for use with the method of the present invention are compounds which are able to accept an electron pair, ie. co-ordinate with an electron donor. Suitable Lewis
 5 acidic compounds include transition metal complexes, alkaline earth metal compounds and other metal based compounds wherein the metal centre can accept an electron pair. Examples of suitable Lewis acids include AlCl_3 , Me_3Al , $\text{MeAl}(\text{OPh})_2$, MAD (methyl aluminum bis(2-6-di-tert-butyl-4-methyl phenoxide)), BF_3 , BBr_3 , BCl_3 , $\text{Ln}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3$, TiCl_4 , FeCl_3 , ZnCl_2 , zinc silicate, calcium silicate, aluminium silicate,
 10 zirconocene dichloride (herein after referred to as (i)), trialkylborates (RO_3B , wherein each R is an alkyl group which can be the same or different), (S,S)- and (R,R)-(+)-N,N'-bis(3,5-di-tert-butylsalicydene)-1,2-diaminocyclohexamanganese (III) chloride (hereinafter referred to as, (ii) and (iii) respectively) (Jacobson's catalyst, Jacobsen *et al.*, *J. Am. Chem. Soc.*, 1991, **113**, 7063).

15

Preferably, the Lewis acid has a solubility, under the reaction conditions employed, of at least about 0.1 molar equivalents, more preferably at least about 0.5 molar equivalents, still more preferably at least about 1.0 molar equivalent, most preferably about 2.0 molar equivalents, per mole of prochiral carbon centred radicals to be reduced.

20

Preferred Lewis acids are those which are alkaline earth metal compounds.

Preferably, the alkaline earth metal compound is a Lewis acidic magnesium compound.

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Examples of suitable Lewis acidic magnesium compounds include MgBr_2 , MgI_2 , $\text{Mg}(\text{OAc})_2$ and $\text{Mg}(\text{OTf})_2$. It will be appreciated that the above list of magnesium compounds is not exhaustive and that the invention encompasses the use of other Lewis acidic magnesium compounds or combinations thereof.

5

The use of MgBr_2 as a Lewis acid in accordance with the present invention has a particular advantage in that it is cheap and readily available.

Accordingly, where the Lewis acid used in accordance with the method of the present
10 invention is a Lewis acidic magnesium compound, the Lewis acidic magnesium compound is preferably MgBr_2 .

Those skilled in the art will appreciate that Lewis acids can often be conveniently provided in the form of a Lewis adduct, that is an adduct formed from a Lewis acid and a Lewis
15 base. In particular, those skilled in the art will appreciate that a Lewis adduct can be used as a convenient source for providing a Lewis acid to a reaction. Accordingly, Lewis acids used in accordance with the present invention may also be provided in the form of a Lewis adduct. For example, Lewis acids such as BF_3 , ZnCl_2 , and MgBr_2 may be provided and used in the form of their diethylether adducts $\text{BF}_3 \cdot \text{Et}_2\text{O}$, $\text{ZnCl}_2 \cdot (\text{Et}_2\text{O})_2$ and $\text{MgBr}_2 \cdot (\text{Et}_2\text{O})_2$,
20 respectively.

The germane is preferably used in an amount of about 0.5-1.5 molar equivalents, more preferably about 1.1 molar equivalents per mole of reductive sites on the substrate, ie central prochiral carbon atoms, to effect optimum reductive conversion.

25

In general, the Lewis acid is preferably used in an amount of about 0.9 to about 2.0 molar equivalents, more preferably in an amount of about 0.9 to about 1.1 molar equivalents, per mole of reductive sites on the substrate, ie central prochiral carbon atoms. In particular, the Lewis acid is preferably used in an amount of about 1.5 molar equivalents, most preferably
30 about 1.0 molar equivalents, per mole of reductive sites on the substrate, ie central prochiral carbon atoms. Lesser amounts can be used such as 0.1 or 0.5 molar equivalents

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although lower enantiomeric excesses (ees) are usually observed. The addition of higher amounts of Lewis acid can also be used, although this does generally not result in an increase in observed ees.

- 5 When the Lewis acid is an alkaline earth metal compound, it is preferable that the Lewis acid is used in an amount of about 1.5 molar equivalents, more preferably about 2.0 molar equivalents, per mole of prochiral carbon centred radicals to be reduced. In particular, when the Lewis acid is a magnesium compound, it is preferable that the Lewis acid is used in an amount of about 1.5 molar equivalents, more preferably about 2.0 molar equivalents,
10 per molecule of prochiral carbon centred radicals to be reduced.

The stereochemistry of the reduced prochiral carbon centre in the resulting compound can be R or S.

- 15 The methods of the invention may be particularly useful in preparing optically enhanced amino acids. Thus, α - or β -carbon centred radicals derived from α - or β -substituted amino acids may be reduced by the methods of the invention to produce optically enhanced amino acids which may be natural or unnatural, including alanine, asparagine, cysteine, glutamine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine,
20 tryptophan, tyrosine, valine, aspartic acid, glutamic acid, arginine, histidine, lysine and their homo derivatives. Other examples include α - and β - straight and branched chain alkyl substituted amino acids, α - and β -cycloalkyl substituted amino acids, and α - and β -aryl substituted amino acids

- 25 The chiral germanes contemplated by the present invention may also be immobilized onto a solid support, eg a polymeric support, such as pins, beads or wells, for use in the methods of the invention, eg used in combinatorial techniques known in the art.

- The present invention provides for a novel class of chiral non-racemic organogermanium
30 organogermanium hydride of general formula (I):

- 19 -



where L_1 , L_2 and L_3 are organic substituents which may be the same or different, and where at least one of L_1 , L_2 and L_3 is chiral, with the proviso that formula (I) is not 4-*tert*-butyl-3,5-dithia-4-germacyclohepa[2,1- α ; 3,4- α']dinaphthalene or 4-*tert*-butyl-2,6-bis(trimethylsilyl)-3,5-dithia-4-germacyclohepa[2,1- α ; 3,4- α']dinaphthalene.

Preferably, the organic substituents L_1 , L_2 and L_3 of general formula (I) are not derived from 1,1'-binaptho-2,2'-dithiol or 3,3'-bis(trimethylsilyl)-1,1'-binaptho-2,2'-dithiol.

10

Preferably, the chiral non-racemic organogermanium hydrides of general formula (I) have a non-chiral germanium atom and therefore derive their chirality from at least one chiral organic substituent. There is no particular limitation as to how the organic substituent(s) derives its chirality, although it is preferred that the chirality is derived from a chiral atom, such as a chiral carbon atom, which forms part of the molecular structure of the substituent.

Where one or two of L_1 , L_2 and L_3 are not chiral, they may be selected from any achiral organic substituents. Suitable achiral ligands include, but are not limited to, optionally substituted aryl (eg. optionally substituted phenyl, and naphthyl) and optionally substituent achiral alkyl (eg. methyl, and butyl) as defined previously.

Generally, L_1 , L_2 and L_3 each form a single covalent bond with the germanium atom of general formula (I). However, L_1 , L_2 and L_3 may form part of a bidentate or tridentate ligand in which case general formula (I) may be represented as $L_{1-2}L_3GeH$ or $L_{1-2-3}GeH$, respectively.

Preferably, at least one of L_1 , L_2 and L_3 of general formula (I) is an organic substituent selected from the group of naturally occurring chiral organic compounds, or the so called chiral pool. Those skilled in the art will appreciate the diverse array natural chiral organic compounds that exist, and those which could be selected for use in accordance with the

30

- 20 -

present invention. By "naturally occurring chiral organic compounds" is meant those chiral compounds which have been identified as occurring in nature. Reference to naturally occurring chiral organic compounds is however not intended to limit such compounds to those which are obtained from a natural source. For example, the natural
5 chiral compounds may be prepared by a synthetic process.

Suitable classes of chiral organic compounds from which at least one of L₁, L₂ and L₃ may be selected, include, but are not limited to, terpenes and their derivatives (eg. menthol, fenchol, pinene etc.), steroids and their derivatives (eg. cholestanol, cholane, cortisone
10 etc.), carbohydrates and their derivatives, including mono, di, tri and polysaccharides, as well as cyclodextrins, amino acids, peptides, proteins and their derivatives, as well as alkaloids and their derivatives as well as numerous biological metabolites and their derivatives. Some of these compounds may form part of the chiral pool.

15 Exemplary chiral organic compounds include, but are not limited to, menthyl, 3 α -cholestanyl, 3 α -24-norcholanyl, 7 α -24-norcholanyl, tetra-O-acetylglucosyl, tetra-O-benzylgalactosyl, gamma-cyclodextrinyl, phenylglycyl, leucyl and morphyl. Some of these compounds may also form part of the chiral pool.

20 A preferred chiral organic compound is menthyl, and preferred organogermanium hydride reagents of general formula (I) are (1R,2S,5R)-menthyl diphenylgermanium hydride (c) and its enantiomer (1S,2R,5S)-menthyl diphenylgermanium hydride (c').

There are a limited number of synthetic pathways known to prepare chiral germanes.
25 Generally, the analogous tin compounds are prepared by reacting a chiral organometallic reagent with a triorganotin halide compound. The resulting chiral tetraorganotin compound is then converted into the tin hydride reagent by means well known in the art. The use of a triorganotin halide in such a procedure is particularly preferred given the well known difficulties associated with using higher halide substituted tin compounds. In
30 particular, a controlled reaction of organometallic reagents with a tin tetrahalide is difficult. For example, the reaction of 1 mole of an organometallic reagent with 1 mole of

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tin tetrachloride fails to yield a mono-organotin trichloride compound as a major product, and instead yields a relatively even mixture of mono-, di-, tri- and tetra organo tin compounds. A similar result has been reported for the reaction of methyl grignard with germanium tetrachloride.

5

Attempts to prepare chiral germanes of the present invention by reacting a chiral organometallic reagent with a triorganogermanium halide compound were found to be ineffective. Despite the known tendency for organometallic reagents to react with a germanium tetrahalide in a non-controlled manner, it has now been found that a
10 germanium tetrahalide can actually be used in a controlled and efficient manner to prepare chiral germanes.

Accordingly, in a further aspect of the present invention there is provided a method of preparing a chiral non-racemic organogermanium compound comprising reacting a chiral
15 non-racemic organometallic reagent with a germanium tetrahalide.

Typically, the reaction of the organometallic reagent with the germanium tetrahalide is performed under an inert atmosphere such as nitrogen or argon. The reaction is generally conducted in an inert solvent, typically an ether solvent such as tetrahydrofuran or
20 diethylether. Depending upon the organometallic reagent used, it may be preferable to perform the reaction at a temperature below ambient temperature. Preferably the reaction is performed at temperatures of about 0°C or less, more preferably of about -20°C or less.

A notable feature of the reaction is that the germanium tetrahalide can be substituted with a
25 single chiral organic group in a controlled manner without any significant formation of higher organo-substituted germanium byproducts. Without wishing to be bound by theory, it is believed that the steric bulk of the organometallic reagent used in the reaction plays a role in facilitating the unique selective and controlled substitution of the germanium tetrahalide. With an appreciation for this, those skilled in the art will readily be able to
30 evaluate suitable organometallic reagents that can be used in accordance with this aspect of the present invention.

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In a preferred embodiment of this aspect, about 1 mole of the chiral organometallic reagent is reacted with about 1 mole of the germanium tetrahalide to afford a chiral non-racemic mono-organogermanium trihalide compound as the major germanium reaction product.

5

As used herein "major germanium reaction product" means that the product is present in the reaction mixture as the most abundant germanium reaction product.

In another preferred embodiment of this aspect, about 2 mole of the chiral organometallic reagent is reacted with about 1 mole of the germanium tetrahalide to afford a chiral non-racemic di-organogermanium dihalide compound as the major germanium reaction product.

In yet another embodiment of this aspect, about 3 mole of the chiral organometallic reagent is reacted with about 1 mole of the germanium tetrahalide to afford a chiral non-racemic tri-organogermanium halide compound as the major germanium reaction product.

Preferably, the mono-organogermanium trihalide, di-organogermanium dihalide and tri-organogermanium halide compounds prepared in accordance with the method are formed in at least a 40% yield, more preferably in at least a 50% yield, and most preferably in at least a 65% yield.

The organometallic reagents used in accordance with the method are nucleophilic in nature and can readily react with halide substituted compounds such as a germanium tetrahalide. Those skilled in the art will appreciate the range of organometallic reagents that could be used in accordance with the present invention. For example, the reagents can include, but are not limited to, lithium, sodium, potassium and magnesium (Grignard) organometallic reagents. Preferably, the organometallic reagent is a Grignard reagent.

30 The organometallic reagents may be prepared by means well known in the art. Typically, the reagents will be derived from a suitable organohalide compound.

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Preferably, the organo group of the organometallic reagent is selected from menthyl, 3 α -cholestanyl, 3 α -24-norcholanyl, 7 α -24-norcholanyl, tetra-O-acetylglucosyl, tetra-O-benzylgalactosyl, gamma-cyclodextrinyl, phenylglyciny, leuciny and morphiny groups.

5 In this case, the organometallic reagent is also preferably a Grignard reagent.

The method of this aspect of the invention utilises a germaniumtetrahalide compound. The halide component of the compound may be either I, Br, Cl or F. Preferably the halide component of the compound is Cl.

10

The method of this aspect of the invention provides a chiral non-racemic organogermanium compound. Accordingly, the compound must contain at least one chiral substituent. It will therefore be appreciated that the method can also be used to attach non-chiral substituents to the germanium compound. In this case, a non-chiral organometallic

15 reagent is used in place of the chiral organometallic reagent.

Having prepared the chiral non-racemic organogermanium compound, the compound can be conveniently converted to a chiral non-racemic organogermanium hydride reagent by methods known in the art. For example, the method of this aspect of the invention may be used to prepare a triorganogermanium halide compound, wherein at least one of the three organo groups is a chiral organo group. This triorganogermanium halide may then be reacted with a reducing agent such as lithium aluminium hydride (LiAlH₄) to afford a chiral non-racemic organogermanium hydride reagent.

20

25 Alternatively, the method may be used to prepare a tetraorganogermanium compound, wherein at least one of the organo groups is a chiral organo group. The tetraorganogermanium compound can then be halogenated to afford a triorganogermanium halide compound which can be converted to a chiral non-racemic organogermanium hydride reagent in a manner described above. In this case, at least one of the organo groups is preferably a phenyl group. Phenyl groups that are attached to a germanium atom can generally be readily replaced by a halide atom such as Br or Cl.

30

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The invention will now be described with reference to the following non-limiting examples and drawing which are included for the purpose of illustrating the invention only and are not to be construed as limiting the generality hereinbefore described.

5

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 (a) shows a representation of the crystal structure of (-)-menGePh₃.

Figure 1 (b) shows a representation of the crystal structure of (+)-menGePh₃.

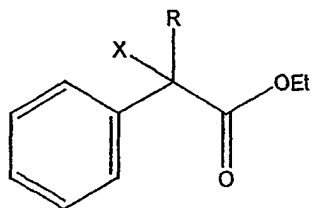
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EXAMPLES

Example 1Reduction of compounds (1a)-(1b), (2a)-(2b), 3, 4 and 5.

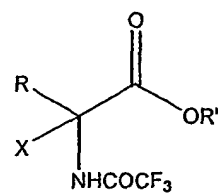
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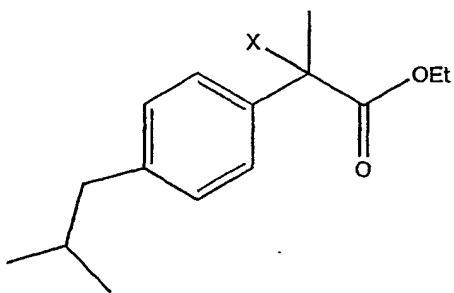
1a. R = Me, X = Br

1b. R = Et, X = Br

10

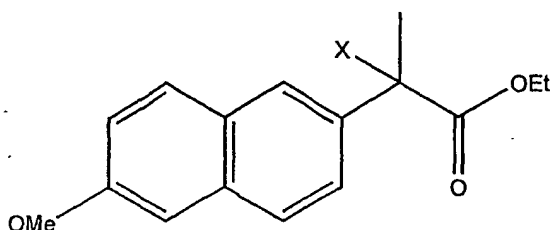
2a. R=tert-Bu,
R'=Benzyl, X = Br2b. R=Ph,
R'=Me, X=Br

15

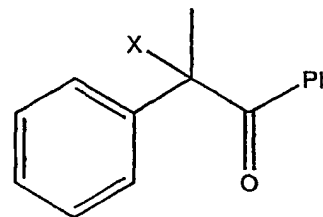


3. X=Br

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4. X=Br



5. X=Br

5 Compounds (1a), (1b), (2a), (2b), and (3-5) (X=Br) were prepared as follows:

Preparation of compounds (1a), (1b) and (5) (X=Br)

Compounds (1a), (1b) and (5) (X=Br) were prepared according to the methods of
 10 Metzger *et al Angew. Chem., Int., Ed. Engl.*, 1997, 36, 235 and Curran, *et al, Tetrahedron: Asymmetry*, 1996, 7, 2417.

Preparation of compound (2a, X=Br)

15

A mixture of racemic *tert*-leucine (0.2g), dry methanol (0.5ml), triethylamine (0.3ml) and methyl trifluoroacetate (0.16ml) was allowed to stir at room temperature for 15 hours. Removal of methanol *in vacuo* afforded the triethylammonium salt of N-trifluoroacetyl-*tert*-leucine as a crystalline mass which was dissolved in dry DMF (0.5ml).
 20 Triethylamine (0.14ml) and benzyl chloride (0.35g) were added and the mixture allowed to stir at room temperature for 40 hours. The resulting mixture was poured into ethyl acetate, washed with H₂O, 5% HCl, sat. NaHCO₃ and brine. The organic layer was dried (MgSO₄) and the solvent removed *in vacuo* to obtain the crude product as a light yellow oil. Pure N-trifluoroacetyl-*tert*-leucine benzyl ester was obtained as a pale oil after flash
 25 chromatography (96:4 hexane: ethyl acetate) in 65% yield.

N-bromosuccinimide (NBS) (61mg) was added to a solution of N-trifluoroacetyl-*tert*-

- 27 -

leucine benzyl ester (100mg) in carbon tetrachloride (5ml). The mixture was irradiated (under reflux) by a 250W tungsten lamp for 45 minutes. The solid was removed by filtration and the solvent removed *in vacuo* to afford (2a, X=Br) in quantitative yield and of sufficient purity for further use.

5

Preparation of compound (2b, X = Br).

The N-trifluoroacetyl amino acid methyl esters (2b, X = H) (100 mg), prepared as described above, were dissolved in carbon tetrachloride (5ml) and N-bromosuccinimide
10 (NBS) (1 equiv) was added. The mixture was irradiated (under reflux) by a 250W tungsten lamp for 45 minutes. The solid was removed by filtration and the solvent removed *in vacuo* to afford (2b, X = Br) in quantitative yield and of sufficient purity for further use.

Preparation of compound (3, X=Br)

15

Racemic ibuprofen (0.5g, 2.42 mmol) and bromine (0.425g, 1.1eq, 2.66mmol) were heated under reflux and PBr₃ (0.67g, 1.03eq, 2.49mmol) slowly added to the reaction mixture. The reaction mixture was further heated at 65-70° until the evolution of HBr had ceased (approx. 3 hours). The reaction mixture was then distilled to remove residual HBr and low
20 boiling impurities. A 1:1 mixture of ethanol/dichloromethane (5ml) was slowly added followed by a small amount of H₂SO₄ (approx 1 drop) and the reaction mixture was heated at reflux for a further 2 hours. The remaining solvent was removed *in vacuo* to afford (3, X=Br) in sufficient purity for further use (0.265g).

25 Preparation of racemic 2-bromonaproxen ethyl ester (4, X = Br)

A solution of commercially available racemic naproxen (0.92g, 4.0 mmol) in thionyl chloride (5mL) was refluxed until the evolution of the HCl gas had ceased (ca. 4 h). The excess thionyl chloride was removed *in vacuo* and a 1:1 mixture of ethanol
30 (3mL):dichloromethane (3mL) was added with refluxing for further 2h. The solution was

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cooled and the solvent removed *in vacuo* to give naproxen ethyl ester as a colourless oil (1.03g, 80%) after purification via flash chromatography (96:4) (hexane: ethyl acetate).

5 N-bromosuccinimide (NBS) (0.33g, 1.85mmol) was added to a solution of the previously-prepared racemic naproxen ethyl ester (0.470g, 1.85mmol) in carbon tetrachloride (5.0mL) and the reaction mixture irradiated (under reflux) by a 250W tungsten lamp for 15 minutes. After cooling in ice, the solid was removed by filtration and the solvent removed *in vacuo* to afford the title racemic bromoester in quantitative yield and of sufficient purity for further use.

10

General reduction procedure

Reductions were carried out in toluene at -78°C . The reaction solution comprised the substrate at a concentration of approximately 0.1M, about 1.1 molar equivalents, relative to the substrate, of the required germane and the Lewis acid of choice in either about 1.0 or 2.0 molar equivalents, relative to the substrate, depending on the Lewis acid chosen (see Table 1). Reactions were initiated with $\text{Et}_3\text{B}/\text{O}_2$. Reactions were carried out until TLC analysis indicated no change in the reaction (ca. 8h) at which time the reaction mixtures were examined by chiral-phase gas chromatography (CG) and the percentage conversion and enantiomeric ratios determined by integration of the signals corresponding to the mixture of reduced compounds 1-5 ($\text{X} = \text{H}$) against an internal standard (either octane or undecane). Reduced compounds 1-5 ($\text{X} = \text{H}$) were identified by comparison of their GC retention times with those of the authentic compounds. Gas Chromatographic analyses of the reaction mixtures were carried out using a chiral trifluoroacetylated γ -cyclodextrin (ChiraldexTM G-TA, 30m x 0.25mm) capillary column purchased from Alltech. The absolute configuration of the dominant isomer in each case was assigned by comparison with the GC retention times of the (S)-products (1a) and (1b) ($\text{X}=\text{H}$), prepared and resolved following a literature procedure (Campbell, A., *et al*, *J. Chem. Soc.*, 1946, 25; Aaron, C., *et al*, *J. Org. Chem.*), the (S)-product (5, $\text{X}=\text{H}$) was prepared and resolved following a literature procedure (Perchyonok, V.T., Schiesser, C.H., *Phosphorous Sulfur*

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Silicon Relat. Elem., 1999, 150151, 193), and the (S)-products (2a), (2b), and 3 (X=H), prepared by the following procedures:

Preparation of (S)-N-trifluoroacetyl-tert-leucine benzyl ester (2a, X = H)

5 A mixture of (S)-tert-leucine (0.2g), dry methanol (0.5ml), triethylamine (0.3ml) and methyl trifluoroacetate (0.16ml) was allowed to stir at room temperature for 15 hours. Removal of methanol *in vacuo* afforded the triethylammonium salt of N-trifluoroacetyltert-leucine as a crystalline mass which was dissolved in dry DMF (0.5ml).
10 Triethylamine (0.14ml) and benzyl chloride (0.35g) were added and the mixture allowed to stir at room temperature for 40 hours. The resulting mixture was poured into ethyl acetate, washed with H₂O, 5% HCl, sat. NaHCO₃ and brine. The organic layer was dried (MgSO₄) and the solvent removed *in vacuo* to obtain the crude product as a light yellow oil. Pure (S)-N-trifluoroacetyl-tert-leucine benzyl ester was obtained as a pale oil after flash
15 chromatography (96:4 hexane: ethyl acetate) in 65% yield.

Preparation of (2b, X = H).

Commercially available racemic phenylglycine (1g) was stirred overnight at room
20 temperature in dry methanol (3ml) containing trimethylsilyl chloride (Me₃SiCl) (3-5 equivalents). The solvent was removed *in vacuo* to obtain the corresponding amino acid methyl ester hydrochloride as a white solid with no need for further purification.

Triethyl amine (1.1eq) was added to a stirred solution of the amino acid methyl ester
25 hydrochloride and methyl trifluoroacetate (1.5 equivalents) in dry methanol (10 ml). The reaction was heated under reflux for 12 hours, after which the solvent was removed and resulting residue redissolved in ether (20ml). The solution was washed with sat. ammonium chloride, dried (MgSO₄) and the ether removed *in vacuo* to obtain the corresponding required N-trifluoroacetyl amino acid methyl ester of sufficient purity for
30 further use.

Preparation of (S)-Ibuprofen methyl ester (3, X = H)

A solution of commercially available (S)-ibuprofen (2g, 9.66mmol) in thionyl chloride (10ml) was heated at reflux until the evolution of gas ceased. The excess thionyl chloride was removed *in vacuo* and solution of ethanol (5ml) in dichloromethane (10 ml) was added and refluxing continued for further 2 hour. The mixture was cooled and the solvent removed *in vacuo* to give (3, X = H) as colourless oil (1.61g, 71%) and of sufficient purity for further use.

Table 1 lists enantioselectivity data for substrates 1 – 5 used in this study reacting with (1R, 2S, 5R)-menthyldiphenylgermanium hydride (c), and its enantiomer (c') at -78° in toluene and in the presence of about 1 – 2 molar equivalents of a Lewis acid, relative to the substrate.

TABLE 1

Enantioselectivities observed for reactions involving (1R, 2S, 5R)-menthyldiphenyl germanium hydride (c), and its enantiomer (c') at -78° in toluene. $\text{MgBr}_2 \cdot (\text{Et}_2\text{O})_2$ was used in about 2 molar equivalents and all other Lewis acids were used in about 1 molar equivalents, relative to the substrate.

| Entry | Substrate | Germane | Lewis Acid | %ee (yield) |
|-------|-----------|---------|---|---------------|
| 1 | 1a | c' | None | 0% (20%) |
| 2 | 1a | c' | $\text{MgBr}_2 \cdot (\text{Et}_2\text{O})_2$ | 10% (30%) |
| 3 | 1b | c' | None | 0% (20%) |
| 4 | 1b | c' | $\text{MgBr}_2 \cdot (\text{Et}_2\text{O})_2$ | 10% (30%) |
| 5 | 2a | c | none | 10% (S) (20%) |
| 6 | 2a | c | $\text{MgBr}_2 \cdot (\text{Et}_2\text{O})_2$ | 80% (S) (20%) |
| 7 | 2a | c' | none | 5% (R) (15%) |
| 8 | 2a | c' | $\text{MgBr}_2 \cdot (\text{Et}_2\text{O})_2$ | 90% (R) (20%) |
| 9 | 2b | c | none | 0% (20%) |
| 10 | 2b | c | $\text{MgBr}_2 \cdot (\text{Et}_2\text{O})_2$ | 99% (S) (40%) |
| 11 | 2b | c' | $\text{MgBr}_2 \cdot (\text{Et}_2\text{O})_2$ | 99% (R) (50%) |

| | | | | |
|----|----|----|---|---------------|
| 13 | 2b | c' | MgI(ClO ₄) ₂ | 15% (R) (35%) |
| 14 | 2b | c' | MAD* | 17% (R) (15%) |
| 15 | 2b | c' | Ln(OTf) ₃ | 11% (R) (45%) |
| 16 | 2b | c' | Yb(OTf) ₃ | 13% (R) (30%) |
| 17 | 2b | c' | calcium silicate | 12% (R) (30%) |
| 18 | 3 | c | none | 10% (S) (30%) |
| 19 | 3 | c | MgBr ₂ ·(Et ₂ O) ₂ | 99% (S) (30%) |
| 20 | 4 | c | none | 10% (S) (30%) |
| 21 | 4 | c | MgBr ₂ ·(Et ₂ O) ₂ | 99% (S) (30%) |
| 22 | 4 | c' | none | 5% (R) (20%) |
| 23 | 4 | c' | MgBr ₂ ·(Et ₂ O) ₂ | 99% (R) (15%) |
| 24 | 5 | c | none | 10% (S) (35%) |
| 25 | 5 | c | MgBr ₂ ·(Et ₂ O) ₂ | 99% (S) (30%) |

*MAD = methyl aluminium bis(2,6-di-tert-butyl-4-methyl phenoxide)

Typical procedure for small-scale low-temperature germane reductions:

- 5 A flask fitted with a septum was charge with a solution of the required bromide (0.3 mmol) and internal standard (octane or decane, 0.3 mmol) in toluene (0.5 mL) followed by Et₃B (0.05ml of 1M solution in THF) and O₂ was introduced.. The solution was cooled to -78°, the flask purged with nitrogen and the required germane (c or c') (0.11 mmol) in toluene (0.5 mL) added. The reaction mixture was stirred for 8 hours, with an additional amount
- 10 of triethylborane (0.05 mL of a 1M solution in THF) added every 2 hours. The solution was warmed to room temperature and analyzed directly by GC.

Typical preparative-scale examples:

- 15 Reduction of benzyl N-trifluoroacetyl-2-bromo-tert-leucinate (2a, X = Br) with (1S, 2R, 5S)-menthylphenylgermanium hydride (c').

Magnesium bromide etherate (MgBr₂·Et₂O) (0.308g, 1.19mmol) was added to dry toluene (3 mL) and the mixture allowed to stir for 30 min under N₂. The bromoester (2a, X = Br) (0.236g, 0.60 mmol) in dry toluene (1 mL) was added slowly to the reaction mixture which

20 was allowed to stir at RT for further 10 min prior to cooling to -78°C. After stirring at -78° for a further 45 min, (1S, 2R, 5S)-menthylphenylgermanium hydride (c') (0.241g,

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0.66mmol) in toluene (1 mL) was added slowly, followed by triethylborane (0.15mL of 1M solution in THF) and oxygen was introduced. The reaction mixture was stirred at this temperature for a further 8 hours. Additional triethylborane (0.15ml of 1M solution in THF) was added to the reaction mixture every 2 hours and after 8 hours there was no further change as evidenced by TLC. The mixture was quenched with water (5 mL) and extracted with ether (2x). The organic layer was dried (MgSO₄) and excess solvent removed *in vacuo* to afford the crude product as light yellow oil. Further purification of the product (flash chromatography, 96:4 hexane/ ethyl acetate) yielded benzyl (*R*)-*N*-trifluoroacetyl-2-bromo-*tert*-leucinate (2a, X = H) as a colourless oil (0.037g, 20%yield).

10 ¹H (NMR) CDCl₃: δ 7.2 (5H, m), 7.6 (1H, s(br)), 5.3 (2H, m), 4.5 (1H, d, *J* 8 Hz), 1.0 (9H, s), α^{13.7}_D(c=0.4, CHCl₃) = -8.3, 90%ee (GC).

Reduction of 2-bromonaproxen ethyl ester (4, X = Br) with (1*S*, 2*R*, 5*S*)-menthyldiphenylgermanium hydride (c').

15 Magnesium bromide etherate (MgBr₂.Et₂O) (0.36g, 1.38mmol) was added to dry toluene (3 mL) and the mixture allowed to stir for 30 min under N₂. The bromoester (4, X = Br) (0.246g, 0.690 mmol) in dry toluene (0.2 mL) was added slowly to the reaction mixture which was allowed to stir at RT for further 10 min prior to cooling to -78°C. After stirring

20 at -78° for a further 45 min, (1*S*, 2*R*, 5*S*)-menthyldiphenylgermanium hydride (c') (0.36g, 0.715mmol) in toluene (3 mL) was added slowly, followed by triethylborane (0.2mL of 1M solution in THF) and oxygen was introduced. The reaction mixture was stirred at this temperature for a further 8 hours. Additional triethylborane (0.2ml of 1M solution in THF) was added to the reaction mixture every 2 hours and after 8 hours there was no further

25 change as evidenced by TLC. The mixture was quenched with water (2 mL) and extracted with ether (2x). The organic layer was dried (MgSO₄) and excess solvent removed *in vacuo* to afford the crude product as light yellow oil. Further purification of the product (flash chromatography, 96:4 hexane/ ethyl acetate) yielded benzyl (*R*)-naproxen ethyl ester (4, X = H) as a colourless oil (0.027g, 15%yield, 99%ee). ¹H (NMR) CDCl₃: δ 7.8-7.1

30 (6H, m), 4.1 (2H, m), 3.9 (3H, s), 3.8 (1H, q), 1.6 (3H, d), 1.4 (3H, t). α_D¹⁴ (c=0.12, CHCl₃) = -32.6 (R), 99%ee.

Procedure for the preparation of (1R,2S,5R)-menthylgermanium hydride (c)

Preparation of (1R, 2S, 5R)-(-)-menthylgermanium trichloride

- 5 A solution of Grignard prepared from (1R,2S,5R)-menthyl chloride (8.15 g, 46.6 mmol) and Mg (1.25 g, 51.3 mmol) in 50 mL of thf was added via cannula to a magnetically stirred solution of GeCl_4 (10.00 g, 46.6 mmol) in 100 mL of Et_2O at -20°C . The reaction mixture was allowed to warm to room temperature and stirred overnight. After filtering and removing the solvent *in vacuo* distillation at 94°C and 5 Pa gave the title compound as
- 10 a colourless liquid (7.4 g, 50% yield). $[\alpha]_{\text{D}}^{25} -51.3^\circ$ ($c = 1$, CHCl_3). ^1H NMR (299.98 MHz, CDCl_3): $\delta = 0.87$ (d, 3H, CH_3), 0.96 (d, 3H, CH_3), 0.99 (d, 3H, CH_3), 1.00-1.26 (m, 2H), 1.14-1.24 (m, 1H), 1.62-1.86 (m, 4H), 1.96-2.08 (m, 1H), 2.13-2.23 (m, 1H), 2.38-2.50 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.44 MHz, CDCl_3): $\delta = 15.33$ (CH_3), 21.51 (CH_3), 22.30 (CH_3), 25.30 (CH_2), 31.36 (CH), 34.07 (CH), 34.24 (CH_2), 36.34
- 15 (CH_2), 44.70 (CH), 50.54 (CH); ESMS (+ve) 341.0 ($\text{M} + \text{Na}$) $^+$. Analysis calcd. for $\text{C}_{10}\text{H}_{19}\text{GeCl}_3$ (318.23): C 37.74, H 6.02; found: C 37.80, H 6.00 %.

Preparation of (1R, 2S, 5R)-(-)-menthyltriphenylgermane

- 20 A solution of Grignard was prepared from PhBr (29.60 g, 188.5 mmol) and Mg (4.58 g, 188.5 mmol) in 200 mL of thf. The solution was filtered while hot through a sintered glass frit to a new flask. (-)-Men GeCl_3 (10.00 g, 31.4 mmol) in 20 mL of thf was added dropwise at room temperature. The reaction mixture was stirred overnight before careful hydrolysis with water. The solvent was removed *in vacuo* and 200 mL Et_2O and 100 mL
- 25 water added. After filtration the organic layer was separated, dried over Na_2SO_4 , filtered and the solvent removed *in vacuo*. Crystallisation from hexane at 4°C gave the title compound as a colourless solid (13.0 g, 93% yield). mp $97-98^\circ\text{C}$. $[\alpha]_{\text{D}}^{25} -34.8^\circ$ ($c = 1$, CHCl_3).
- 30 ^1H NMR (299.98 MHz, CDCl_3): $\delta = 0.77$ (d, 3H, CH_3), 0.82 (d, 3H, CH_3), 0.97 (d, 3H, CH_3), 1.00-1.15 (m, 2H), 1.20-1.35 (m, 2H), 1.40-1.55 (m, 1H), 1.55-1.65 (m, 1H), 1.75-

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2.05 (m, 3H), 2.10-2.30 (m, 1H), 7.40-7.60 (m, 9H, Ph), 7.65-7.85 (m, 6H, Ph); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.44 MHz, CDCl_3): δ = 16.36 (CH_3), 21.58 (CH_3), 22.65 (CH_3), 26.37 (CH_2), 30.81 (CH), 31.47 (CH), 34.66 (CH), 35.21 (CH_2), 39.68 (CH_2), 45.21 (CH), 127.92 (Ph_m), 128.37 (Ph_p), 135.29 (Ph_o), 137.87 (Ph_i); Analysis calcd. for $\text{C}_{28}\text{H}_{34}\text{Ge}$ (443.19): C 75.88, H 7.73; found: C 75.80, H 7.81 %. See Figure 1 and Tables 2 and 3 for crystallography data.

Preparation of (1R, 2S, 5R)-menthylphenylgermanium bromide

10 Bromine (5.06 g, 31.63 mmol) was added to a solution of (-)-MenGePh₃ (14.02 g, 31.63 mmol) in 50 mL of dibromoethane. The solution was stirred overnight at reflux before removing the solvent *in vacuo* to give (-)-MenPh₂GeBr as a pale yellow liquid which was used without purification.

15 ^1H NMR (270.17 MHz, CDCl_3): δ = 0.64 (d, 3H, CH_3), 0.79 (d, 3H, CH_3), 0.89 (d, 3H, CH_3), 0.90-1.30 (m, 3H), 1.30-1.50 (m, 1H), 1.50-1.65 (m, 1H), 1.65-1.90 (m, 3H), 2.00-2.25 (m, 2H), 7.30-7.80 (m, 10H, Ph); $^{13}\text{C}\{^1\text{H}\}$ NMR (67.94 MHz, CDCl_3): δ = 15.68 (CH_3), 21.51 (CH_3), 22.48 (CH_3), 25.83 (CH_2), 30.96 (CH), 34.33 (CH), 34.89 (CH_2), 36.16 (CH), 38.51 (CH_2), 45.13 (CH), 128.26 / 128.34 (Ph_m), 129.68 (Ph_p), 133.70 / 20 133.81 (Ph_o), 137.14 / 136.04 (Ph_i).

Preparation of (1R, 2S, 5R)-menthylphenylgermanium hydride (c)

A solution of (-)-MenPh₂GeBr (10.00 g, 22.4 mmol) in 50 mL Et₂O was added dropwise to 25 a suspension of LiAlH₄ (0.43 g, 11.2 mmol) in 50 mL Et₂O. The reaction mixture was stirred for 1 hour and then hydrolysed with water (50 mL) using ice cooling. After filtration the organic layer was collected and the aqueous layer washed with an additional 50 mL of Et₂O. The combined organic layer was dried over Na₂SO₄, filtered and the solvent removed *in vacuo*. Distillation at 140°C and 1 Pa (Kugelrohr) gave (-)-Men 30 Ph₂GeH as a colourless liquid (7.1 g, 87% yield).

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^1H NMR (299.98 MHz, C_6D_6): δ = 0.73 (d, 3H, CH_3), 0.75 (d, 3H, CH_3), 0.78 (d, 3H, CH_3), 0.82-1.04 (m, 2H), 1.08-1.24 (m, 2H), 1.32-1.44 (m, 1H), 1.50-1.76 (m, 3H), 1.88-1.98 (m, 1H), 1.98-2.14 (m, 1H), 5.31 (s, 1H, GeH), 7.08-7.20 (m, 6H, Ph), 7.52-7.60 (m, 4H, Ph); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.44 MHz, C_6D_6): δ = 15.82 (CH_3), 21.91 (CH_3), 22.81 (CH_3),
 5 26.32 (CH_2), 31.11 (CH), 31.90 (CH), 34.85 (CH), 35.57 (CH_2), 39.86 (CH_2), 45.84 (CH), 128.56 / 128.61 (Ph_m), 129.04 / 129.07 (Ph_p), 135.58 / 135.71 (Ph_o), 136.85 / 136.93 (Ph_i);
 Analysis calcd. for $\text{C}_{22}\text{H}_{30}\text{Ge}$ (367.08): C 71.98, H 8.24; found: C 71.93, H 8.39 %.

Preparation of (1S,2R,5S)-methylgermanium hydride (c') was performed in the same way
 10 as described for (c) except (1S,2R,5S)-methyl chloride was used.

Table 2.

Crystal data and structure refinement for (-)-(1R, 2S, 5R)-menGePh₃ and (+)-(1S, 2R, 5S)-menGePh₃.

15

| | (-)-menGePh ₃ | (+)-menGePh ₃ |
|--|---------------------------------------|---------------------------------------|
| Formula | $\text{C}_{28}\text{H}_{34}\text{Ge}$ | $\text{C}_{28}\text{H}_{34}\text{Ge}$ |
| Formula weight, g mol^{-1} | 443.14 | 443.14 |
| Crystal system | Orthorhombic | Orthorhombic |
| Crystal size, mm | 0.07 x 0.25 x 0.40 | 0.12 x 0.15 x 0.50 |
| Space group | $P2(1)2(1)2(1)$ | $P2(1)2(1)2(1)$ |
| a , Å | 9.3345(6) | 9.3103(7) |
| b , Å | 12.5991(8) | 12.5683(9) |
| c , Å | 20.6109(12) | 20.5599(15) |
| α , ° | 90 | 90 |
| β , ° | 90 | 90 |
| γ , ° | 90 | 90 |
| V , Å ³ | 2424.0(3) | 2405.8(3) |
| Z | 4 | 4 |
| ρ_{calcd} , Mg m^{-3} | 1.214 | 1.223 |
| T , K | 293(2) | 293(2) |
| μ , mm^{-1} | 1.274 | 1.284 |

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| | | |
|--|----------------------|----------------------|
| $F(000)$ | 936 | 936 |
| θ range, deg | 1.9 to 27.5 | 1.9 to 27.5 |
| Index ranges | $-12 \leq h \leq 12$ | $-8 \leq h \leq 12$ |
| | $-16 \leq k \leq 16$ | $-16 \leq k \leq 14$ |
| | $-26 \leq l \leq 26$ | $-17 \leq l \leq 26$ |
| No. of reflns colld | 21093 | 15249 |
| Completeness to θ_{\max} | 99.8% | 99.6% |
| No. of indep reflns/ R_{int} | 5533 | 5505 |
| No. of reflns obsd with ($I > 2\sigma(I)$) | 5161 | 4498 |
| No. refined Params | 262 | 262 |
| GooF (F^2) | 1.097 | 0.953 |
| $R_1 (F)$ ($I > 2\sigma(I)$) | 0.039 | 0.050 |
| $wR_2 (F^2)$ (all Data) | 0.086 | 0.100 |
| $(\Delta/\sigma)_{\max}$ | < 0.00001 | < 0.00001 |
| Flack | 0.004(11) | 0.021(15) |
| Largest diff peak/hole, $e \text{ \AA}^{-3}$ | 0.598 / -0.226 | 0.741 / -0.368 |

Table 3.

Selected bond lengths [\AA] and angles [$^\circ$] for (-)-(1*R*, 2*S*, 5*R*)-menGePh₃ and (+)-(1*S*, 2*R*, 5*S*)-menGePh₃.

| | (-)-menGePh ₃ | (+)-menGePh ₃ |
|-------------------|--------------------------|--------------------------|
| Ge(1)-C(1) | 1.989(3) | 1.982(3) |
| Ge(1)-C(11) | 1.968(3) | 1.967(3) |
| Ge(1)-C(21) | 1.960(3) | 1.955(4) |
| Ge(1)-C(31) | 1.956(3) | 1.950(4) |
| C(1)-Ge(1)-C(11) | 110.06(11) | 109.91(13) |
| C(1)-Ge(1)-C(21) | 115.26(11) | 115.29(13) |
| C(1)-Ge(1)-C(31) | 109.46(11) | 109.21(14) |
| C(11)-Ge(1)-C(21) | 102.31(11) | 102.47(11) |

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| | | |
|-------------------|------------|------------|
| C(11)-Ge(1)-C(31) | 109.97(12) | 110.01(14) |
| C(21)-Ge(1)-C(31) | 109.54(11) | 109.74(15) |

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps
5 but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

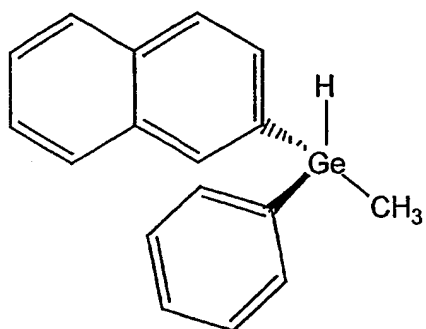
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Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications which fall within the spirit and scope. The invention also includes all of the steps, features, compositions and
15 compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

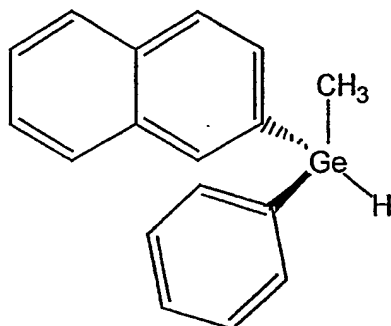
What is claimed

1. A method for enantioselectively reducing a prochiral carbon centred radical having one or more electron donor groups attached directly to the central prochiral carbon atom of the radical, and/or attached to a carbon atom within 1 to 4 atoms of the central prochiral carbon atom, comprising treating said radical with a chiral non-racemic organogermanium hydride in the presence of a Lewis acid.
2. The method of Claim 1, wherein the electron donor group is attached directly to the central prochiral carbon atom or to a carbon atom within 1 or 2 atoms of the central prochiral carbon atom.
3. The method of Claim 1 or Claim 2, wherein the prochiral carbon centred radical is a prochiral amino acid carbon centred radical wherein the central prochiral carbon atom is an α - carbon atom of an α - amino acid or a β - carbon atom of an β -amino acid.
4. The method of any one of Claims 1 to 3, wherein the prochiral carbon centred radical is generated from a radical precursor selected from the group consisting of: aryl selenides, aryl sulphides, aryl tellurides, xanthates, thionoformates, Barton esters and tertiary chiral halosubstrates.
5. The method of any one of Claims 1 to 4, wherein the electron donor group is a carbonyl group.
6. The method of any one of Claims 1 to 5, wherein the organogermanium hydride is selected from the group consisting of:

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(a)



(b)

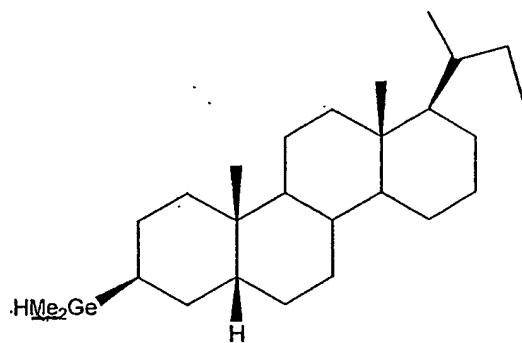
menPh₂GeH

(c)

enan-menPh₂GeH

(c')

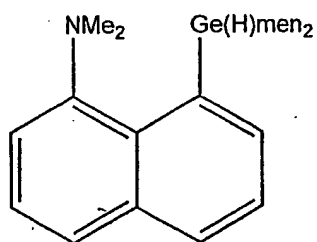
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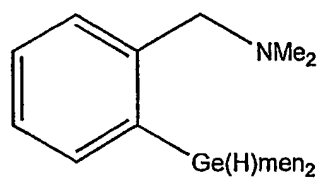
(d)

men₂PhGeH

(e)

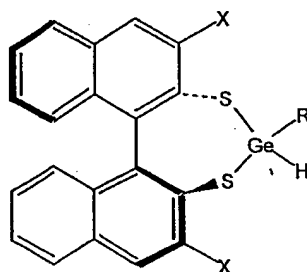


(f)



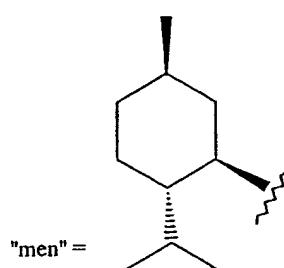
(g)

- 40 -

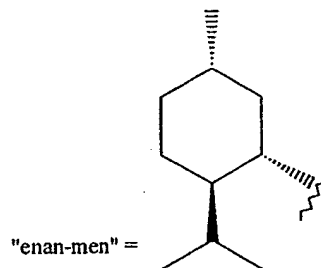


(h)

5 where



and



7. The method of any one of Claims 1 to 6, wherein the Lewis acid is selected from
 10 the group consisting of: AlCl_3 , Me_3Al , $\text{MeAl}(\text{OPh})_2$, MAD (methyl aluminum bis(26-di-
 tert-butyl-4-methyl phenoxide)), BF_3 , BBr_3 , BCl_3 , $\text{Ln}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3$, TiCl_4 , FeCl_3 ,
 ZnCl_2 , zinc silicate, calcium silicate, aluminium silicate, zirconocene dichloride, an
 alkaline earth metal compound, trialkylborates and (S,S)- and (R,R)-(+)-N,N'-bis (3,5-di-
 tert-butylsalicydene)-1,2-diaminocyclohexamanganese (III) chloride.

15

8. The method of Claim 7, wherein the alkaline earth metal compound is a Lewis
 acidic magnesium compound.

9. The method of Claim 8, wherein the Lewis acidic magnesium compound is selected
 20 from the group consisting of MgBr_2 , MgI_2 , $\text{Mg}(\text{OAc})_2$, $\text{Mg}(\text{OTf})_2$.

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10. The method of Claim 9, wherein the Lewis acidic magnesium compound is MgBr_2 .
11. The method of any one of Claims 1 to 10, wherein the Lewis acid is provided in the
5 form of a Lewis adduct.
12. The method of Claim 11, wherein the Lewis adduct is selected from the group consisting of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, $\text{ZnCl}_2 \cdot (\text{Et}_2\text{O})_2$ and $\text{MgBr}_2 \cdot (\text{Et}_2\text{O})_2$.
- 10 13. The method of Claim 12, wherein the Lewis adduct is $\text{MgBr}_2 \cdot (\text{Et}_2\text{O})_2$.
14. The method of any one of Claims 1 to 13, wherein the Lewis acid has a solubility, under the reaction conditions employed, of at least about 0.1 molar equivalents per mole of prochiral carbon centred radicals to be reduced.
15
15. The method of Claim 8, wherein the Lewis acidic magnesium compound has a solubility, under the reaction conditions employed, of about 2 molar equivalents per mole of prochiral carbon centred radicals to be reduced.
- 20 16. The method of any one of Claims 1 to 15, wherein the Lewis acid is used in an amount of about 0.9 to about 2 molar equivalents per mole of prochiral carbon centred radicals to be reduced.
17. The method of Claim 16, wherein the Lewis acid is used in an amount of about 0.9
25 to about 1.1 molar equivalents per mole of prochiral carbon centred radicals to be reduced.
18. The method of Claim 7, wherein the alkaline earth metal compound is used in an amount of about 2 molar equivalents per mole of prochiral carbon centred radicals to be reduced.
30
19. The method of Claim 8, wherein the Lewis acidic magnesium compound is used in

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an amount of about 2 molar equivalents per mole of prochiral carbon centred radicals to be reduced.

20. The method of any one of Claims 1 to 19, wherein the organogermanium hydride is used in an amount of about 0.5 to about 1.5 molar equivalents per mole of prochiral carbon
5 centred radicals to be reduced.

21. The method of any one of Claims 1 to 20, wherein the organogermanium hydride is immobilized onto a solid support.

22. A chiral non-racemic organogermanium hydride of formula (I):



10 where L_1 , L_2 and L_3 are organic substituents which may be the same or different, and where at least one of L_1 , L_2 and L_3 is chiral, with the proviso that formula (I) is not 4-*tert*-butyl-3,5-dithia-4-germacyclohepa[2,1- α ; 3,4- α']dinaphthalene or 4-*tert*-butyl-2,6-bis(trimethylsilyl)-3,5-dithia-4-germacyclohepa[2,1- α ; 3,4- α']dinaphthalene.

23. The organogermanium hydride of Claim 22 wherein the germanium atom is non-
15 chiral.

24. The organogermanium hydride of Claim 22 or Claim 23 wherein each of L_1 , L_2 and L_3 form a single covalent bond with the germanium atom.

25. The organogermanium hydride of any one of Claims 22 to 24 wherein at least one of L_1 , L_2 and L_3 is a chiral organic substituent which contains at least one chiral carbon
20 atom.

26. The organogermanium hydride of any one of Claims 22 to 25 wherein at least one of L_1 , L_2 and L_3 are independently selected from naturally occurring chiral organic compounds.

25 27. A method of preparing a chiral non-racemic organogermanium compound comprising reacting a chiral non-racemic organometallic reagent with a germanium

- 43 -

tetrahalide.

28. The method of claim 27 wherein about 1 mole of the chiral organometallic reagent is reacted with about 1 mole of the germanium tetrahalide to afford a chiral non-racemic
5 mono-organogermanium trihalide compounds as the major germanium reaction product.

29. The method of claim 27 wherein about 2 mole of the chiral organometallic reagent is reacted with about 1 mole of the germanium tetrahalide to afford a chiral non-racemic di-organogermanium dihalide compound as the major germanium reaction product.

10

30. The method of claim 27 wherein about 3 mole of the chiral organometallic reagent is reacted with about 1 mole of the germanium tetrahalide to afford a tri-organogermanium halide compound as the major germanium reaction product.

15 31. The method of any one of claims 27 to 30 wherein the chiral organometallic reagent is a Grignard reagent.

32. The method of any one of claims 27 to 31 wherein the chiral non-racemic organogermanium compound is converted into a chiral non-racemic organogermanium
20 hydride reagent.

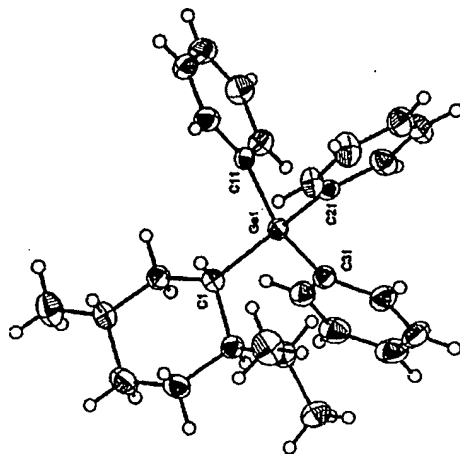
33. The method of claim 32 wherein the chiral non-racemic organogermanium compound is a triorganogermanium halide compound which contains at least one chiral organo group, and wherein the triorganogermanium halide compound is reduced with a
25 reducing agent to thereby convert the compound into the chiral non-racemic organogermanium hydride reagent.

34. The method of claim 32 wherein the chiral non-racemic organogermanium compound is a tetraorganogermanium compound which contains at least one chiral organo
30 group, wherein the tetraorganogermanium compound is halogenated to afford a triorganogermanium halide compound which contains at least one chiral organo group, and

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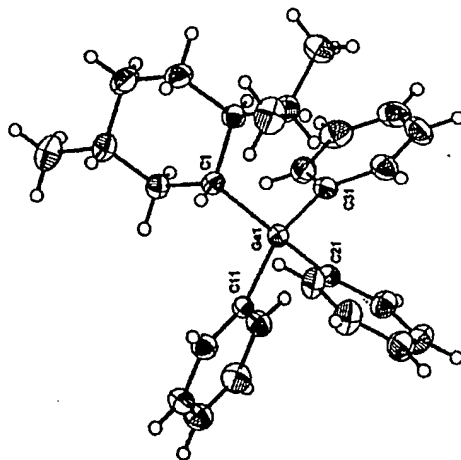
wherein the triorganogermanium halide compound is reduced with a reducing agent to thereby convert the compound into the chiral non-racemic organogermanium hydride reagent.

1/1



(+)-menGePh₃
[α]_D²⁵ +37.1° (c = 1, CHCl₃)

1(b)



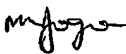
(-)-menGePh₃
[α]_D²⁵ -34.8° (c = 1, CHCl₃)

1(a)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU03/00902

| A. CLASSIFICATION OF SUBJECT MATTER | | |
|---|---|--|
| Int. Cl. ⁷ : C07F 7/30 | | |
| According to International Patent Classification (IPC) or to both national classification and IPC | | |
| B. FIELDS SEARCHED | | |
| Minimum documentation searched (classification system followed by classification symbols) SEE BELOW | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched SEE BELOW | | |
| Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN (CA; REG): sub-structure of claim 22 | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X,Y | Organometallics 17, pp 1687-99 (1998) Tacke et al "Enzymatic transformation and liquid-chromatographic separation as methods for the preparation of the (R) and (S)-enantiomers of the centrochiral hydrido-germanes $p\text{-XC}_6\text{H}_4(\text{H})\text{Ge}(\text{CH}_2\text{OAc})\text{CH}_2\text{OH}$ (X=H, F)"; see Abstract and pp 1690-1693 | 1-34 |
| X,Y | J Organometallic Chem 65, pp 343-348 (1974) Carre et al "Stereochemie des reactions de substitution des alcoxy-germanes par les organolithiens et par les reactifs de Grignard". See Summary and page 345. | 1-34 |
| X,Y | J Organometallic Chem 25, pp 395-402 (1970) Carre et al "Synthese et compartement d'un nouvel organogermane optiquement actif, l'isopropylphenyl-1-naphtylgermane". See pp 396-399. | 1-34 |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input type="checkbox"/> See patent family annex | | |
| <p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> | | |
| Date of the actual completion of the international search 11 August 2003 | | Date of mailing of the international search report 13 AUG 2003 |
| Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. (02) 6285 3929 | | Authorized officer  MADHU K. JOGIA Telephone No : (02) 6283 2512 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU03/00902

| C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|---|---|-----------------------|
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | J Organometallic Chem 14, pp 505-507 (1968) Peddle et al "Stereochemical crossover in hydrogen-hydrogen exchange at silicon". See whole document | 1-34 |
| X | J Organometallic Chem 37, pp 267-74 (1972) Eaborn et al "Organometallic Compounds XI. The stereochemistry of the reactions of optically active ethyl(1-naphthyl)phenylgermylithium with some carbonyl compounds". See Summary and Table 1. | 1-34 |
| X | Tetrahedron 37, pp 1141-1151 (1981) Dubac et al "Stereochemie de reactions au niveau des liaisons silicium (ou germanium)-phosphore dans le systeme dimethyl-1,2 sila (ou germa) cyclopentanique". See whole document. | 1-34 |
| X | J Chem Soc Perkin Trans II, pp7-13 (1988) Takeuchi et al "Nuclear magnetic resonance spectra of organogermanium compounds. Part 4. Nuclear magnetic resonance spectra and molecular mechanics calculations of germacyclohexane, methylgermacyclohexanes, and dimethylgermacyclohexanes". See Scheme, p 8. | 1-34 |
| X | Bull Chem Soc Jpn 63, pp 708-715 (1990) Takeuchi et al "NMR spectra of organogermanium compounds. IX. NMR spectra and molecular mechanics calculations of 1-t-butylgermacyclohexanes". See page 708 | 1-34 |
| X | Chemical Communications, p 1581 (1971) Sakurai et al "The optical stability of a chiral germyl radical". | 1-34 |